PRE-ORGANIZED TRICYCLIC INTEGRASE INHIBITOR COMPOUNDS

This non-provisional application claims the benefit of Provisional Application No. 60/418,963, filed October 16, 2002, and Provisional Application No. 60/478,783, filed June 16, 2003, which are incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates generally to compounds with antiviral activity and more specifically with HIV-integrase inhibitory properties.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) infection and related diseases are a major public health problem worldwide. A virally encoded integrase protein mediates specific incorporation and integration of viral DNA into the host genome. Integration is necessary for viral replication. Accordingly, inhibition of HIV integrase is an important therapeutic pursuit for treatment of HIV infection of the related diseases.

Human immunodeficiency virus type 1 (HIV-1) encodes three enzymes which are required for viral replication: reverse transcriptase, protease, and integrase. Although drugs targeting reverse transcriptase and protease are in wide use and have shown effectiveness, particularly when employed in combination, toxicity and development of resistant strains have limited their usefulness (Palella, etal *N. Engl. J. Med.* (1998) 338:853-860; Richman, D. D. *Nature* (2001) 410:995-1001). There is a need for new agents directed against alternate sites in the viral life cycle. Integrase has emerged as an attractive target, because it is necessary for stable infection and homologous enzymes are lacking in the human host (LaFemina, etal *J. Virol.* (1992) 66:7414-7419). The function of integrase is to catalyze integration of proviral DNA, resulting from the reverse transcription of viral RNA, into the host genome, by a stepwise fashion of endonucleolytic processing of proviral DNA within a cytoplasmic preintegration complex (termed 3'-processing or "3'-P") with specific DNA sequences at the end of the HIV-1 long terminal repeat (LTR) regions, followed by translocation of the complex into the nuclear compartment where integration of 3'-processed proviral DNA into host DNA occurs in a "strand

transfer" (ST) reaction (Hazuda, etal *Science* (2000) 287:646-650; Katzman, etal *Adv. Virus Res.* (1999) 52:371-395; Asante-Applah, etal *Adv. Virus Res.* (1999) 52:351-369). Although numerous agents potently inhibit 3'-P and ST in extracellular assays that employ recombinant integrase and viral long-terminal-repeat oligonucleotide sequences, often such inhibitors lack inhibitory potency when assayed using fully assembled preintegration complexes or fail to show antiviral effects against HIV-infected cells (Pommier, etal *Adv. Virus Res.* (1999) 52:427-458; Farnet, etal *Proc. Natl. Acad. Sci. U.S.A.* (1996) 93:9742-9747; Pommier, etal *Antiviral Res.* (2000) 47:139-148.

Certain HIV integrase inhibitors have been disclosed which block integration in extracellular assays and exhibit good antiviral effects against HIV-infected cells (Anthony, etal WO 02/30426; Anthony, etal WO 02/30930; Anthony, etal WO 02/30931; WO 02/055079; Zhuang, etal WO 02/36734; US 6395743; US 6245806; US 6271402; Fujishita, etal WO 00/039086; Uenaka etal WO 00/075122; Selnick, etal WO 99/62513; Young, etal WO 99/62520; Payne, etal WO 01/00578; Jing, etal *Biochemistry* (2002) 41:5397-5403; Pais, etal *Jour. Med. Chem.* (2002) 45:3184-94; Goldgur, etal *Proc. Natl. Acad. Sci. U.S.A.* (1999) 96:13040-13043; Espeseth, etal *Proc. Natl. Acad. Sci. U.S.A.* (2000) 97:11244-11249).

HIV integrase inhibitory compounds with improved antiviral and pharmacokinetic properties are desirable, including enhanced activity against development of HIV resistance, improved oral bioavailability, greater potency and extended effective half-life *in vivo* (Nair, V. "HIV integrase as a target for antiviral chemotherapy" *Reviews in Medical Virology* (2002) 12(3):179-193). Three-dimensional quantitative structure-activity relationship studies and docking simulations (Buolamwini, etal *Jour. Med. Chem.* (2002) 45:841-852) of conformationally-restrained cinnamoyl-type integrase inhibitors (Artico, etal *Jour. Med. Chem.* (1998) 41:3948-3960) have correlated hydrogen-bonding interactions to the inhibitory activity differences among the compounds.

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g. to neighboring cells, is often difficult or inefficient.

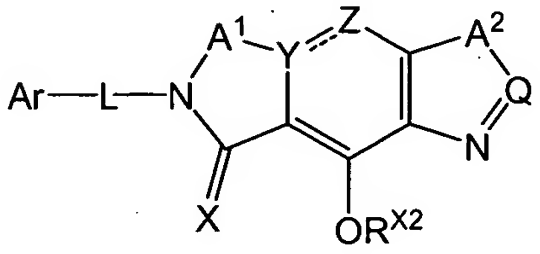
Most agents currently administered parenterally to a patient are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often

undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., cytotoxic agents and other anti-cancer or anti-viral drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g. blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells. Intracellular targeting may be achieved by methods and compositions which allow accumulation or retention of biologically active agents inside cells.

SUMMARY OF THE INVENTION

The present invention provides compositions and methods for inhibition of HIV integrase.

In one aspect, the invention is a compound having the structure:

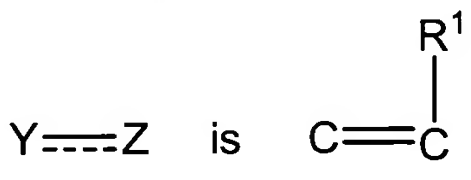


wherein:

A^1 is independently selected from $C(R^2)_2$, CR^2OR, $CR^2OC(=O)R$, $C(=O)$, $C(=S)$, CR^2SR, and $C(=NR)$,

A^2 is independently selected from $C(R^2)_2$–$C(R^3)_2$, $C(R^2)=C(R^3)$, and $C(=O)C(R^3)_2$;

Q is CR^4;



;

L is selected from a bond, O, S, S–S, $S(=O)$, $S(=O)_2$, $S(=O)_2NR$, NR, N–OR, C_1–C_{12} alkylene, C_1–C_{12} substituted alkylene, C_2–C_{12} alkenylene, C_2–C_{12} substituted alkenylene, C_2–C_{12} alkynylene, C_2–C_{12} substituted alkynylene, $C(=O)NH$, $OC(=O)NH$, $NHC(=O)NH$, $C(=O)$, $C(=O)NH(CH_2)_n$, or $(CH_2CH_2O)_n$, where n is optionally 1, 2, 3, 4, 5, or 6;

X is selected from O, S, NH, NR, N–OR, $N–NR_2$, $N–CR_2OR$ and $N–CR_2NR_2$;

Ar is selected from (a) a C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl;

or (b) a saturated, unsaturated or aromatic ring or ring system having a mono- or bicyclic carbocycle or heterocycle containing 3 to 12 ring atoms;

R^2, R^3 and R^4 are each independently selected from H, F, Cl, Br, I, OH, $-NH_2$, $-NH_3^+$, $-NHR$, $-NR_2$, $-NR_3^+$, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, $-SO_2R$, $-SO_2Ar$, $-SOAr$, $-SAr$, $-SO_2NR_2$, $-SOR$, $-CO_2R$, $-C(=O)NR_2$, 5-7 membered ring lactam, 5-7 membered ring lactone, $-CN$, $-N_3$, $-NO_2$, C_1–C_8 alkoxy, C_1–C_8 trifluoroalkyl, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

when taken together on a single carbon, two R^2 or two R^3 may form a spiro ring; R^1 is independently selected from CR_3, $NRSO_2R$, $OC(=O)NR_2$ $OC(=O)R$, SR, H, F, Cl, Br, I, OH, $-NH_2$, $-NH_3^+$, $-NHR$, $-NR_2$, $-NR_3^+$, C_1–C_8 alkylhalide, carboxylate, sulfate, sulfamate, sulfonate, 5-7 membered ring sultam, C_1–C_8 alkylsulfonate, C_1–C_8 alkylamino, 4-dialkylaminopyridinium, C_1–C_8 alkylhydroxyl, C_1–C_8 alkylthiol, $-SO_2R$, $-SO_2Ar$, $-SOAr$, $-SAr$, $-SO_2NR_2$, $-SOR$, $-CO_2R$, $-C(=O)NR_2$, 5-7 membered ring lactam, 5-7 membered ring lactone, $-CN$, $-N_3$, $-NO_2$, C_1–C_8 alkoxy, C_1–C_8 trifluoroalkyl, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_3–C_{12} carbocycle, C_3–C_{12} substituted carbocycle, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

R is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, and a prodrug moiety;

R^{X2} is independently selected from H, C_1–C_8 alkyl, C_1–C_8 substituted alkyl, C_6–C_{20} aryl, C_6–C_{20} substituted aryl, C_2–C_{20} heteroaryl, and C_2–C_{20} substituted heteroaryl, polyethyleneoxy, phosphonate, phosphate, a prodrug moiety, and a protecting group;

and the tautomers, salts, solvates, resolved enantiomers and purified diastereomers thereof;

with the proviso that when Y=Z is C=C(OH), X is O, A^1 is C(=O), A^2 is $C(R^2)=C(R^3)$, and Q is CH, then L is not a bond.